Rejections Under 103(a)

Claims 16-23 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Russell et al., Druker et al., and Kaufman. Applicants respectfully traverse.

Jellis et al. concerns a phage display library and discloses unique nucleic acids encoding approximately $1.5x10^8$ unique peptides of 20 amino acids fused to coat proteins for display on the surface of phage particles. The emphasis in Jellis is the creation of unique peptides with minimal amino acid bias.

Druker et al. disclose a small collection of retroviruses with point mutations in the polyoma middle T antigen gene. However, Druker characterizes his methodology as "tedious":

> It is clear that the mutagenesis techniques used in these studies is relatively tedious and has not been widely used. See page 6860, second column, first sentence of last paragraph.

Arguably, this teaches away from using this technique in other applications.

Kaufman is a general reference about a variety of mammalian expression vectors. Kaufman teaches that retroviral vectors can be used to transduce genes into a variety of host cell types, often with high efficiency, and that genes so introduced may incorporate into the host genome.

Russell et al. is concerned with the presentation of a non-viral protein moiety, particularly an antibody fragment with predetermined affinity for a given hapten, as a component of a fusion protein with a viral glycoprotein on the surface of retroviruses. Russell et al. is solely concerned with "display packages", e.g. viruses that contain fusions of non-viral polypeptides to at least part of a glycoprotein; see definition at column 11, lines 62-67:

> The term viral display package is used to mean a recombinant viral particle capable of infecting eukaryotic cells, comprising a non viral polypeptide coupled to at least part of a glycoprotein and displayed on the external surface of the particle, and nucleic acid encoding the non-viral polypeptide and said at least part of a viral glycoprotein.

Thus, the Examiner's citation of Russell for motivation (column 16, lines 62-64) must be taken in the context in which Russell meant: that retroviral display packages (e.g. those containing fusions to glycoproteins) could be used analogously to phage display libraries. This, however, does not suggest the use of retroviruses to deliver libraries of random peptides that are not fused to retroviral glycoproteins to cells.

As stated in the MPEP at §2143, in order to support a *prima facie* case of obviousness under 35 U.S.C. §103(a), the prior art, either individually or in combination, must satisfy the following three elements:

> 1) there must be some motivation or suggestion, either in the references or in the knowledge available to one skilled in the art, to modify or combine the references to practice the claimed invention; and
>
> 2) there must be a reasonable expectation of success; and
>
> 3) the prior art references when combined must teach or suggest all of the claim limitations.

In view of these requirements, Applicant respectfully submits that the cited prior art references do not render the present invention obvious.

The Examiner states that it would have been obvious to create a peptide library in retroviral vectors. The Examiner suggests that the disclosure of Russell et al. would motivate one of reasonable skill in the art to combine and/or modify the cited references in order to practice the present invention. The Office Action states:

> One would have been motivated with a reasonable expectation of success by the desire to create only a single library of vector-borne peptides in order to use the same library both for the screening process and for the stable transformation of mammalian cells for expression of the desired peptides and by the teaching of the '287 patent (Russell et al.) that retroviral display packages could be used for applications analogous to those of a phage display library.

Applicants disagree.

First, the Examiner asserts that the motivation to combine or modify the cited references in order to practice the instant invention is provided by a desire to create a single library with the hypothetical utility set forth by Russell et al. as well as utility in a

screening method and a method of stable transformation. However, neither Russell et al. nor the remaining cited references suggest the screening process set forth in the present specification, for which the claimed molecular library compositions are designed, nor the stable transformation of mammalian cells with a library, a means to the end of the claimed mammalian cell library compositions. Thus the motivation the Examiner relies upon to arrive at the molecular libraries of retroviruses set forth by the instant invention is not provided by cited references and knowledge in the art, but rather stems from the instant disclosure.

In addition, as acknowledged by the Examiner, Jellis et al. does not disclose libraries of retroviruses or cells containing the libraries. Druker does not add any motivation, and as cited above, actually teaches away from using his technique in other applications. Kaufman is a general reference that does not add any motivation for the creation of random peptide libraries. Russell, as argued above, is limited to discussions regarding fusions with viral glycoproteins for display libraries.

In conclusion, none of the cited references, taken alone or in combination, provides the motivation to make retroviral random peptide libraries.

With particular regard to new claim 29, none of the references teach or suggest libraries of cells containing retroviruses expressing libraries of intracellular random peptides.

Even assuming, arguendo, that the motivation exists, there is no reasonable expectation of success. Russell et al. teach away from the present practice. Particularly, Russell et al. teach away from retroviral libraries. Russell et al. suggest hypothetical uses for retroviral peptide display libraries, but temper their suggestions based on quantitative limits they foresee for the technology. Particularly, Russell et al. concede at column 17 line 9:

> The theoretical maximum achievable retroviral display library size does not compare favorably with the theoretical maximum size of a bacteriophage display library. It is therefore unlikely that retrovirus display libraries will challenge the established applications of phage display libraries such as in vitro antibody selection and affinity maturation.

Essentially Russell et al. suggest that retroviral peptide display libraries analogous to bacteriophage peptide display libraries cannot be synthesized. Attempts to do so would in their opinion result in a less pluralistic population of viral display particles which would likely not be of the same use as bacteriophage libraries. In this way, Russell et al. teach away from retroviral libraries comprising large numbers of randomized nucleic acids encoding a plurality of peptides. This teaching is furthered in the specification, where examples suggest that useful peptides be first identified in bacteriophage libraries and subsequently used in retroviral display particles, rather than identified in retroviral libraries themselves.

In the absence of scientific support for the feasibility of arriving at the retroviral libraries posited by Russell et al., and given the teaching away from the instant invention by Russell et al., the reasonably skilled artisan would not have a reasonable expectation of success in arriving at the instant invention given the cited references and knowledge available in the art at the time of filing.

Conclusion

Applicant's submit that the cited art does not teach or suggest all of the limitations of Claims 21, 23, and 28, that motivation or suggestion to combine or modify the cited references to practice the claimed invention is not provided by the references or by knowledge in the art, and that a reasonable expectation of success in arriving at the instant invention is not provided. Accordingly, Claims 16-23 and 28 are not obvious under 35 U.S.C. §103(a), and Applicants request withdrawal of the rejection.

Rejection concerning Nilsson

Claims 16-28 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Russell et al., Druker et al., Kaufman, and Nilsson et al. Applicants respectfully traverse.

Jellis et al. , Russell et al., Druker et al., and Kaufman are discussed supra.

Nilsson et al. teaches the construction of fusion proteins for a variety of purposes. However, Nilsson et al. does not teach or suggest the use of fusion proteins in retroviral libraries with random peptides.

The Examiner states that it would be *prima facie* obvious to combine the teachings of Nilsson with the other references, based on Nilsson's teachings that fusion proteins can be constructed for a variety of reasons. However, this is not the standard for obviousness; in fact, Nilsson does not teach or suggest the combination of fusion proteins with random peptides in retroviral libraries.

CONCLUSION

Applicants respectfully request favorable consideration of the preceding arguments and acceptance of the claims as currently pending. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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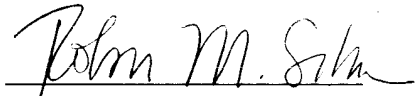

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APPENDIX:

16. (Amended) A molecular library of retroviruses comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

17. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^5 different randomized nucleic acids encoding a plurality of randomized peptides.

18. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^6 different randomized nucleic acids encoding a plurality of randomized peptides.

19. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^7 different randomized nucleic acids encoding a plurality of randomized peptides.

20. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^8 different randomized nucleic acids encoding a plurality of randomized peptides.

21. (Amended) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said molecular library comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

22. A cellular library according to claim 21 wherein said constructs are integrated into the cellular genome.

23. A molecular library of retroviruses according to claim 16, wherein said nucleic acids further encode a fusion partner.

24. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a targeting sequence.

25. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a rescue sequence.

26. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a stability sequence.

27. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a dimerization sequence.

28. A molecular library of retroviruses according to claim 16, wherein said randomized n nucleic acids are biased in their randomization.

29. A cellular library of mammalian cells containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides.